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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,573	02/08/2001	Etienne Regulier	017753-137	5075

7590 10/03/2005

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/762,573	REGULIER ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

Claims 33-57 are pending.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/7/05 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amendment to claim 33 (and claims dependent therefrom) filed on 9/7/05 introduces new subject matter into the application.

The application and the originally filed claims as a whole are directed to a composition comprising: (i) a nucleic acid sequence encoding all or part of an MIP chemokine, (ii) at least

one nucleic acid sequence encoding IL-2, said nucleic acid sequence being placed under the control of elements required for the expression in a host cell of said mammal and using the composition to treat a proliferative disorder in a patient.

The original specification and claims do not disclose the limitation: wherein the IL-2 and MIP chemokine or a natural variant of MIP1-alpha or MIP-1beta provide an improved anti-tumor response in said patient when compared to the anti-tumor response in said patient administered with a composition comprising a vector comprising only the nucleic acid sequence (i) or the nucleic acid sequence (ii) in the instant claims. The limitation is broader than the description set forth in the specification. The pages cited for support of the limitation in claims 33-44 do not provide support for the limitation. See Page 3 and Figures 1-6. On page 3, the applicants state, "We have now identified novel cytotoxic compositions in which the various constituents are chosen so to obtain a synergistic effect of their respective activities and improved properties of said constituents." However, the specification does not describe what is a synergistic effect and how it correlates to an improved anti-tumor response using a nucleic acid encoding all or part of a MIP chemokine or a natural variant of MIP1-alpha or MIP-1beta and a nucleic acid encoding at least Il-2. On page 3, the specification further does not specifically point out what cytotoxic composition produces a synergistic effect. Furthermore, the working examples do not disclose a composition comprising a nucleic acid sequence encoding a genus of MIP chemokines or a natural variant thereof of MIP1 alpha or MIP1beta and a nucleic acid sequence encoding IL-2, wherein the IL-2 and MIP chemokine provide an improved anti-tumor response compared to a composition comprising a vector comprising only the nucleic acid sequence encoding IL-2 or a vector comprising only the nucleic acid sequence encoding MIP.

The specification only provides description for using a nucleic acid encoding MIP-1 alpha or MIP-1 beta with a nucleic acid encoding IL-2. It is apparent that the applicants at the time the invention was made did not intend or contemplate the claimed invention as part of the disclosure of their invention. There is no evidence in the specification that the applicants were possession of the claimed method, where IL-2 and a genus of MIP chemokines working together to provide an improved anti-tumor response, at the time the application was filed.

Applicants' arguments filed 9/7/05 have been fully considered but they are not persuasive.

In response to applicant's arguments that page 3 and the working examples provide support for the new limitation in claim 33 (and claims dependent therefrom), the arguments are not found persuasive because the instant specification only provides support for using a nucleic acid encoding either MIP-1alpha or MIP-1beta and a nucleic acid encoding IL-2 in the claimed method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 33-36 and 41-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over LaFace (US 6,649,158) taken with Boursnell et al. (US Patent 6,287,557) and Hobart et al. (US Patent 6,147,055). LaFace teaches a method of administering a composition to induce killing of tumor cells (column 3). LaFace teaches the use of genetic adjuvants such as cytokines, to mobilize dendritic cells and induce differentiation and activation, as well as chemokines to direct immature dendritic cells to the tumor site and mature dendritic cells to the lymph nodes may be essential to achieve consistently effective anti-tumor immunity and regression (column 3). LaFace teaches transduction of tumor cells with p53 and chemokine (MIP-3-alpha) (column 12). LaFace further teaches that the composition may also include a cytokine gene (column 15). The cytokine gene can be selected from Il-1, Il-2, Il-4, Il-12, Il-10, Il-19, Il-20, interferons of the alpha, beta, and gamma subtypes (column 11). The term "dendritic cell chemoattractant" (DCC) refers to chemokines selected from MIP-1alpha, MIP-1beta, MIP-3alpha, MIPbeta (column 11).

LaFace teaches using a replication defective adenoviral vector, wherein the vector's E1 region is deleted (columns 6-7). However, LaFace does not specifically teach directly administering to tumor cells a composition comprising a nucleotide sequence encoding IL-2 and a nucleotide sequence encoding a MIP1-beta to kill a tumor in a mammal.

However, at the time the invention was made, Boursnell teaches virus vectors encoding nucleotide sequences expressing immunomodulating proteins including cytokines and chemokines and combinations thereof (col. 6, lines 55-67), such as IL-2 and MIP1β (col. 7, lines 1-11) for cancer immunotherapy, wherein each of the sequences are placed under control of a known viral promoter or a mammalian specific promoter (col. 9, lines 45-51). Boursnell further teaches making and using a vector comprising two or more nucleotide sequences or a mixture of two vectors containing at least one gene encoding a different immunomodulator product (col. 8, lines 50-55). Furthermore, Boursnell teaches a method of using the vector for cancer immunotherapy in an animal by direct administration (col. 11, lines 8-67). The vector can be a mutant DNA or RNA virus, e.g., adenovirus, poxvirus (col. 5, lines 49-55). The vectors used in the method taught by Boursnell are in pharmaceutically acceptable formulas.

In addition, at the time the invention was made, Hobart teaches a method of treating a solid tumor in an animal comprising introducing a vector comprising IL-2 into the solid tumors (col. 4, lines 33-41, col. 4, line 66- col. 5, and col. 33, line 33 to col. 36, line 37). Interleukin 2 (IL-2) is an important cytokine in the generation of anti-tumor immunity (column 1). In response to tumor antigens, helper T-cells secrete local amounts of IL-2. This IL-2 acts locally at the site of tumor antigen stimulation to activate cytotoxic T-cells (CTL) and natural killer cells (NK), cellular immune activity which may mediate systemic tumor cell destruction (column 1).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of LaFace taken with Boursnell and Hobart to directly administer a composition comprising a nucleotide sequence encoding IL-2 and a nucleotide sequence encoding an MIP1 to inhibit tumor growth in a patient. One of ordinary skill in the art would have been motivated to combine the teachings because a nucleotide sequence encoding IL-2 and a nucleotide sequence encoding MIP were well known to one of ordinary skill in the art for treating a tumor in an animal. In addition, direct administration of the nucleic acids to a tumor is a routine route of administration for one of ordinary skilled in the art to efficiently deliver nucleic acids as exemplified by Boursnell. One of ordinary skill in the art would have been motivated to select IL-2 as the cytokine because Il-2 acts locally at the site of tumor antigen as exemplified by Hobart (column 1). Therefore, it would have been obvious to one of ordinary skill in the art to make and use the composition in a method of treating a tumor in a patient in need thereof.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of LaFace taken with Boursnell and Hobart to use a nucleotide sequence encoding IL-2 and a nucleotide sequence encoding a natural variant of either MIP1alpha or MIP1beta in the claimed method. One of ordinary skill in the art would have been motivated to combine the teachings because LaFace teaches that any known chemokine can be used in the method to kill tumors in vivo. In addition, the instant specification does not define what is considered to be a natural variant of either MIP1alpha or MIP1beta and a nucleic acid encoding MIP3 would read on the natural variant because MIP has a structural similarity to either MIP and all three MIPs are DCCs.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of LaFace taken with Boursnell and Hobart to insert a nucleotide sequence encoding IL-2 and a nucleotide sequence encoding MIP1 into the same vector. One of ordinary skill in the art would have been motivated to insert both sequences into the same vector to simplify delivering the sequences to a cell and because Boursnell teaches that it was routine to one of ordinary skill in the art to use one vector comprising two different nucleotide sequences in a cancer immunotherapy method.

Furthermore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of LaFace taken with Boursnell and Hobart to insert a nucleotide sequence encoding IL-2 and a nucleotide sequence encoding MIP1 into distinct vectors. One of ordinary skill in the art would have been motivated to insert both sequences into different vectors because Boursnell teaches that it was routine to one of ordinary skill in the art to use two different vectors comprising two different nucleotide sequences in a cancer immunotherapy method.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of LaFace taken with Boursnell and Hobart to use a composition comprising a nucleotide sequence encoding IL-2 and a nucleotide sequence encoding a MIP1, wherein the composition is inserted into a recombinant adenovirus vector. One of ordinary skill in the art would have been motivated to combine the teachings because recombinant adenoviral vectors comprising an anti-tumor gene were well known to one of ordinary skill in the art for reducing tumors in an animal. Therefore, it would have been obvious

to one of ordinary skill in the art to make and use the adenoviral vector comprising the nucleotide sequences in a cancer immunotherapy method.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to make and use a replication defective adenoviral vector taught by Bruder in the method taught by LaFace taken with Boursnell and Hobart. One of ordinary skill in the art would have been motivated to use a replication defective adenoviral vector because they are superior vehicles for transferring genetic material to a wide variety of cells and represent a safe choice of gene transfer. In addition, one of ordinary skill in the art would have been motivated to use a multiply deficient adenoviral vector (E1-) to abolish expression of the adenoviral proteins (E1) to improve the delivery of exogenous nucleic acid sequences to an animal.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 9/7/05 have been fully considered but they are not persuasive.

Applicants argue that Boursnell cites IL-2, MIPalpha and MIP1-beta along with more than 40 other immunomodulating polypetides and no motivation is provided to the skilled artisan to choose the combination as presently claimed. See Ex parte A, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990).

In response to Applicant's argument that there is no motivation provided by the cited references to arrive at the claimed subject matter. None of the cited references contain an indication that a method associating IL-2 and MIP-encoding nucleic acid sequences would

provide an effective anti-tumor response. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 916 F.2d680, 16 USPQ2d 1430 (Fed. Cir. 1990). See also In re Fritch, 972 F.2d 1260, 23 USPQ2d 1780. Although the motivation need not be explicit, the motivation must be present to combine the prior art references in a manner to solve the problem. See Ruiz v. A.B. Chance Co., 69 U.S.P.Q.2d 1686, 1690-91 (Fed. Cir. 2004).

Applicant's argument is not found persuasive because the cited references teach that MIP and IL-2 encoding nucleic acid sequences can be used to treat tumors in a mammal. See LaFace (column 13) and Hobart (columns 3-4). See In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

In response to applicant's argument that Boursnell's method is prophetic and is not entitled to a presumption of operability, the argument is not found persuasive because. when the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

In response to applicant's argument that in view of the teaching of LaFace, the skilled artisan would not have been motivated to associate a nucleic acid encoding MIP-1 alpha with a nucleic acid encoding Il-2 because the reference teaches the skilled artisan to pursue the association of MIP-1 alpha with a cytokine such as Il-4 or GM-CSF in order to improve

differentiation dendritic cells differentiation, the argument is not found persuasive because LaFace further teaches that cytokine can be selected from several interleukins including Il-2 (column 11).

Claims 33-38, 45, 50-54, and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over LaFace (US 6,649,158) taken with Boursnell et al. (US Patent 6,287,557) and Hobart et al. (US Patent 6,147,055) as applied to claims 33-36 and 41-52 above, and further in view of in further view of Bruder et al. (US Patent 6,440,944).

LaFace taken with Boursnell and Hobart do not specifically teach making a replication defective adenoviral vector, wherein said adenoviral vector is deleted in the E1 and E4, or E1 and E3, or E1, E3, and E4.

However, at the time the invention was made, replication defective adenoviral vectors were well known to one of ordinary skill in the art for gene delivery because they are superior vehicles for transferring genetic material to a wide variety of cells and represent a safe choice of gene transfer. Bruder teaches that a variety of recombinant adenoviral vectors are known in the art for gene delivery (col. 1, lines 34-55). Bruder teaches an adenoviral vector with a gene of interest inserted into the E1 region of the adenovirus. Furthermore, Bruder teaches multiply deficient adenoviral vectors that are deficient in E1, E3 and E4. One of ordinary skill in the art understands that a recombinant adenoviral vector is replication defective because genes essential for adenovirus replication are deleted.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to make and use a replication defective adenoviral vector taught by

Bruder in the method taught by LaFace taken with Boursnell and Hobart. One of ordinary skill in the art would have been motivated to use a replication defective adenoviral vector because they are superior vehicles for transferring genetic material to a wide variety of cells and represent a safe choice of gene transfer. In addition, one of ordinary skill in the art would have been motivated to use a multiply deficient adenoviral vector (E1-; E1-E4-; and E-1, E3-) to abolish expression of the adenoviral proteins (E1, E3, and/or E4) to improve the delivery of exogenous nucleic acid sequences to an animal.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 9/7/05 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is the case here. The claimed method is already taught by Boursnell, LaFace and Hobart and Bruder is provided to show that using a replication defective adenovirus vector, wherein the vector is missing an E1, E3 and E4 region was well known to one of ordinary skill in the art for delivering a transgene in vivo.

Claims 33, 39, 40, 45, 55, and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over LaFace taken with Boursnell et al. and Hobart et al. (US Patent 6,147,055) as applied to claims 33-36 and 41-52 above, in further view of Gruber (US Patent 6,410,326).

Boursnell taken with Hobart and LaFace do not specifically teach making a poxvirus vector selected from the group consisting of vaccinia virus, MVA, and canary pox.

However, at the time the invention was made, vaccinia virus was well known to one of ordinary skill in the art for expressing heterologous proteins at high levels as taught by Gruber (col. 7, line 65, col.8, line 26).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to make and use vaccinia virus taught by Gruber in the method taught by LaFace, Boursnell and Hobart. One of ordinary skill in the art would have been motivated to make and use a vaccinia viral vector because vaccinia virus vectors were well known to one of ordinary skill in the art for expressing heterologous proteins at high levels in cells.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is the case here. The claimed method is already taught by Boursnell, LaFace and Hobart and Gruder is provided to show that using a vaccinia virus was well known to one of ordinary skill in the art for delivering a transgene in vivo.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE – Art Unit 1635, can be reached at (571) 272-0811.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman
Patent Examiner, Group 1635